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An Organocatalytic Biomimetic Strategy Paves the Way for the Asymmetric Umpolung of Imines

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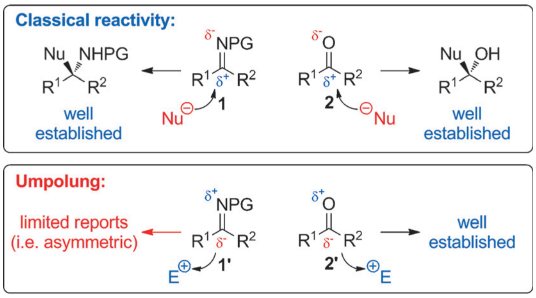
Dedicated to Professor Karl Grubmayr on the occasion of his 65th birthday

According to a recent analysis, significantly more than 80 % of all FDA-approved small-molecule drugs contain at least one nitrogen atom.[1] Considering this extraordinarily high value and keeping in mind the fundamental fact that the three-dimensional arrangement of biologically active molecules is of utmost importance for their interaction with biological targets, it comes as no surprise that for decades, the synthesis of optically active amines has been one of the major motivations for chemists to develop new asymmetric (catalytic) synthetic methods.[2]

Various powerful strategies have been developed in the past, mainly making use of the inherent electrophilicity of prochiral imine **1**, which, upon reaction with nucleophiles (e.g., a hydride donor or a carbon nucleophile), provides access to a broad variety of chiral amine derivatives.[2] In analogy to classical nucleophilic addition reactions to prochiral carbonyl groups **2**, this method has emerged as one of the fundamental (retrosynthetic) strategies in (asymmetric) synthesis. On the other hand, reversing this inherent reactivity by inverting the polarization of these groups enables highly useful complementary assembly strategies, providing access to structures and substitution patterns that are not (or only hardly) accessible by classical methods. This concept is known as umpolung and has very impressively been developed into a rather generally applicable strategy for reactions of carbonyl compounds.[3] In sharp contrast, the umpolung of the reactivity of imines has thus far been less generally addressed,[4] and especially the development of asymmetric variants turned out to be a great challenge (Scheme 1).

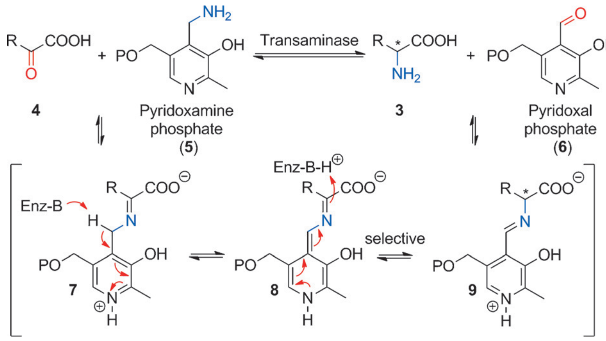
Keeping all these facts in mind, it comes as no surprise that some of the leading groups in the field of asymmetric catalysis recently initiated research programs aiming at the development of catalytic asymmetric umpolung strategies that allow for the use of imine precursors as nucleophilic species.[5–10] In this Highlight, some of the most recently developed organocatalytic biomimetic concepts for the highly enantioselective and high-yielding umpolung of imines are presented.[6–8,10]



Scheme 1. Classical and inverted (umpolung) reactivity of carbonyl compounds **2** and imines **1**.

Before discussing these reports, it is necessary to have a brief look at one of the well-investigated biosynthesis routes towards chiral α-amino acids **3**.[11] Nature has developed a transamination strategy to accomplish the synthesis of amino acids **3** starting from simple α-keto acids **4**. This unique reaction is usually catalyzed by enzymes, so-called transaminases, and makes use of pyridoxamine phosphate (**5**) as the co-factor, which is converted into the corresponding aldehyde **6** in the course of this transformation (Scheme 2).[11]

For a synthesis-oriented chemist, this transformation is especially appealing for two reasons: First, the protonation of the imine carbon atom of the conjugated intermediate **8** represents an inversion of the inherent reactivity of this imine, as the formerly electrophilic imine carbon atom reacts as



Scheme 2. Transamination in the biosynthesis of chiral α-amino acids **3**.

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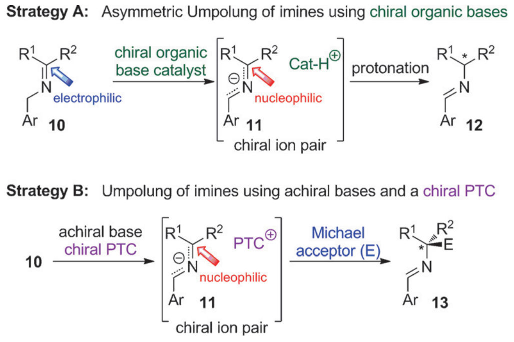
a Brønsted base. Second, this base-catalyzed isomerization of **7** to **9** proceeds with full control of the newly formed stereogenic center, thus resulting in a remarkably efficient and selective biosynthesis of chiral α-amino acids **3**.

However, mimicking this strategy by using non-enzymatic catalysts turned out to be a very challenging task for a long time,[5] and it is not surprising that the development of methods that provide both high yields and high stereoselectivity required lots of efforts, especially with respect to catalyst identification and fine-tuning. Thus, the first highly enantioselective organocatalytic variant of the important transamination reaction was introduced only recently by Shi and co-workers.[6]

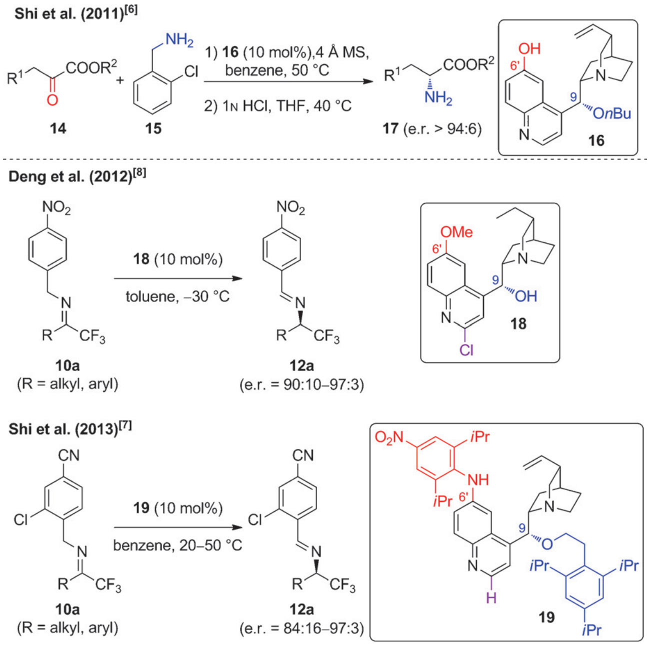
The basic idea was to render this isomerization enantioselective by using a chiral organobase as the catalyst. Such a catalyst is supposed to facilitate the formation of the corresponding 2-azaallyl anion **11**—the actual umpolung step, which makes the imine carbon atom nucleophilic. This achiral anion is now ion-paired with the protonated chiral catalyst, thus allowing for face differentiation in the following protonation step to give the chiral transamination product **12** (Scheme 3, strategy A).



Scheme 3. Two recently introduced strategies for the asymmetric organocatalytic umpolung of imines **10**.

After a very detailed screening of different chiral base catalysts, Shi et al. finally found that the use of cinchona alkaloids containing a free 6′-hydroxy group and a 9-O-alkyl moiety leads to high selectivities in an operationally very simple process starting from α-keto esters **14** using benzylamine **15** for the in situ imine generation (Scheme 4, top).[6] It should be highlighted that with carefully optimized cinchona derivative **16**, this elegant transamination tolerated a variety of different keto esters **14**, giving access to more than 20 of the corresponding amino esters **17** with very high enantioselectivity.

Very soon after this breakthrough report, Shi and co-workers[7] as well as the Deng group[8] more or less simultaneously expanded this method towards the highly enantioselective synthesis of trifluoromethylated amines **12a** (Scheme 4, bottom). Such trifluoromethylated amines are of very high importance with respect to medicinal applications; however, although their synthesis has been extensively investigated, significant challenges still remain (see Refs. [7] and [8], and references therein). Accordingly, the development of complementary, broadly applicable synthetic approaches will be of significant value.



Scheme 4. Shi's seminal report on the use of chiral organobases to facilitate highly enantioselective transamination reactions of α-keto esters **14**[6] and the subsequent reports expanding this method to the synthesis of chiral trifluoromethylated amines **12a**.

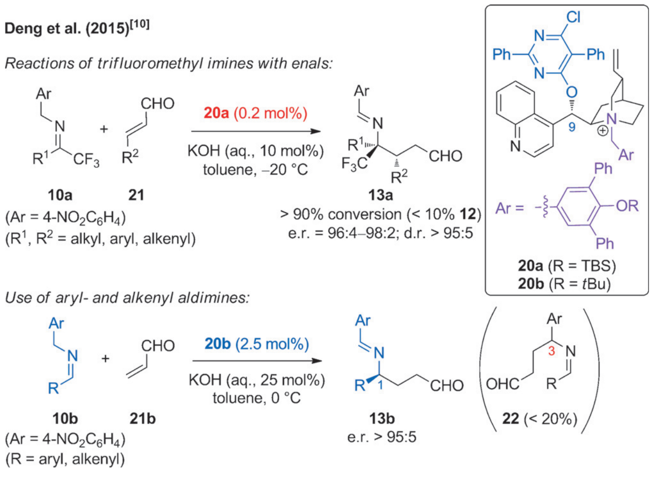
It is very impressive that in both reports, excellent selectivities could be achieved using both aromatic and aliphatic imines **10a** as the starting materials, thus resulting in rather generally applicable synthetic strategies. Interestingly, in both cases, the catalyst had to be very carefully optimized, and finally, the two groups came up with two rather differently substituted, but equally effective cinchona alkaloid catalysts (Scheme 4).

Following the establishment of these powerful transamination methods, where the chiral-base-directed protonation of the intermediate azaallyl anion **11** is the selectivity-determining key step (Scheme 3, strategy A), Deng and co-workers also investigated the enantioselective trapping of this intermediate with Michael acceptors.[10] The use of azaallyl anions as nucleophiles in C−C bond-forming reactions dates back to the early reports in the field of imine/amine umpolung chemistry[4] and allows for unique transformations. However, their use in asymmetric approaches turned out to be rather challenging, and the first truly catalytic and highly selective reports were published only recently, for example, by the Buchwald group (asymmetric Pd catalysis)[9a] and the Kobayashi group (chiral guanidine catalysis).[9b]

Deng and co-workers were the first to succeed in controlling the stereoselective addition of anions **11** to different Michael acceptors by using chiral organocatalysts, resulting in an unprecedented, extremely versatile asymmetric umpolung strategy for simple imine precursors.[10] Upon reading their seminal report, it soon becomes obvious why this reaction is so challenging, and the remarkable efforts made by the authors to develop this strategy into a generally applicable synthetic method are rather impressive. The first severe obstacle that they faced was that the use of chiral base catalysts did not result in any formation of the target product **13**; instead, it always gave the isomerized transamination product **12**.[10] The authors realized that this competing process is highly favored because of the presence of the protonated cinchona alkaloid species formed in situ (see Scheme 3, strategy A), which brings the proton into close proximity to the anion and thus prevents the C–C bond formation. This issue could be successfully overcome by using chiral ammonium salt phase-transfer catalysts[12] together with an inorganic aqueous base (see Scheme 3, strategy B). Under these biphasic conditions, the proton is removed from the organic phase, which results in an ion pair consisting of the azaallyl anion and the chiral quaternary ammonium salt as depicted in Scheme 3, which is then able to undergo the subsequent C–C bond-forming step in a stereoselective fashion.[10] Whereas achiral ammonium salts or structurally simple, commonly used cinchona-based ammonium salts still mainly gave the isomerized imine **12** (with relatively low enantioselectivities for **13**), the protonation could finally be suppressed after a careful optimization of the catalyst structure. The authors realized that the nature of the ammonium group as well as the 9-O-substituent both played an important role with respect to conversion, chemo-, and enantioselectivity: The optimized catalyst **20a** promoted the addition of trifluoromethyl imines **10a** to acceptors **21** with excellent chemo- and stereoselectivity (Scheme 5). Impressively, very low catalyst loadings could be employed (usually 0.2 mol%), and even lower loadings (0.01 mol%) were possible on the gram scale.[11]

Finally, the authors also succeeded in using aryl or alkenyl aldimines **10b** (Scheme 5, bottom). It should be emphasized that the chemoselectivity was very high as only in a few cases, small quantities of the C3-alkylated products **22** could be detected, which highlights the potential of this approach.[10]

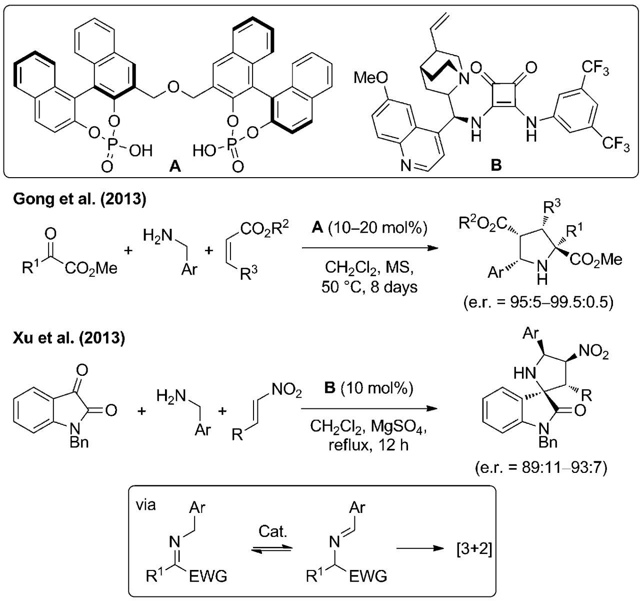
In conclusion, spectacular progress has been made over the last four years in mimicking Nature's transamination strategy by using chiral organocatalysts. Whereas the use of chiral organobase catalysts allows for the synthesis of chiral amines in a highly efficient and straightforward manner, it was very recently shown that such an imine umpolung strategy also allows for the enantioselective addition of simple imines to Michael acceptors by using chiral phase-transfer catalysts. In our opinion, this report represents one of the most impressive recent milestones in modern asymmetric (organo)catalysis, and we are very much convinced that this method will pave the way for new strategies in asymmetric catalysis and will soon be used by other groups.



Scheme 5. Catalytic asymmetric C–C bond-forming umpolung reaction of imines developed by Deng and co-workers.[10]

Addendum

During the publication process we became aware of two very important conceptually related papers published in 2013, which should also be mentioned within the context of this Highlight.[13,14]



In these fundamental reports, the groups of Gong[13] and Xu[14] described biomimetic asymmetric 1,3-dipolar cycloaddition reactions involving the umpolung of simple in situ generated imine species. Whereas Gong et al. were able to control the in situ transamination and the subsequent asymmetric Michael-initiated 1,3-dipolar cycloaddition by using a carefully optimized chiral bisphosphoric acid catalyst,[13] Xu et al. employed a chiral squaramide catalyst to facilitate an analogous reaction with high selectivities and broad scope.[14]

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